C.—Same as method A except a solution of equal volumes of EtOH and diglyme was used as solvent.

D.—To a solution of 0.4 mole of NaOH in 75 ml of H_2O was added 0.2 mole of **2** and 500 ml of diglyme. To this mixture was added 0.2 mole of **1** and the mixture was stirred under reflux for 60 hr. The mixture was cooled, diluted with H_2O, and acidified. The precipitate was filtered, washed (H_2O), dried, and recrystallized.

Substituted 3-(2-Aminophenoxy)-2-chlorobenzoic Acids (4a–z) (Table II).—A solution of **3** in aqueous EtOH was prepared by dissolving **3** in EtOH and adding H_2O until the solution became cloudy (usually 1:1). A 4 g-atom excess of Fe powder was added and the mixture was stirred and heated to reflux. A 9 *M* excess of AcOH was added dropwise and the mixture was heated an additional 1 hr after the addition had been completed. The mixture was cooled to room temperature and made basic with aqueous NH_3. Air was drawn through the stirred mixture for 3–5 hr to ensure complete conversion of the dissolved Fe^{2+} to the more easily filtered $Fe(OH)_3$. The mixture of unreacted Fe and $Fe(OH)_3$ was filtered through a mat of Supercel, and the filter cake was washed thoroughly with dilute aqueous NH_3. The combined filtrates were concentrated to remove EtOH and excess NH_3. The concentrate was acidified carefully with dilute HCl until a drop of acid produced no further precipitation. The solid amino acid was filtered, washed with H_2O, and dried. This material was usually pure enough for the preparation of the N-formyl derivative **5**.

Substituted 2-Chloro-3-(2-formamidophenoxy)benzoic Acids (5a–z) (Table III).—A mixture of **4** and 97–100% formic acid (10 ml/g of **4**) was stirred and refluxed for 2–18 hr (the reaction was followed by tlc using the same system that was used in the preparation of **3**). The solution was cooled and poured into several volumes of H_2O with vigorous stirring. The solid was filtered and washed well with H_2O. The crude product was usually contaminated with trace amounts of unreacted **4** but was sufficiently pure for the next reaction.

Substituted Phenoxazine-1-carboxylic Acids (6a–x) (Table IV). **A.**—A mixture of 0.01 mole of **5**, 0.02 mole of K_2CO_3, 0.1 g of Cu bronze, and 100 ml of dry DMF was stirred and refluxed under N_2 for 30–60 min. The hot mixture was filtered into several volumes of warm H_2O. The filter cake was washed with a small volume of H_2O and the combined filtrates were acidified with dilute HCl. The resulting yellowish green precipitate was cooled, filtered, and redissolved in dilute NH_4OH. The solution was filtered and acidified again. The precipitate was filtered, washed, dried, and recrystallized.

B.—The reaction was carried out as described in A except dry diglyme was used in place of DMF and refluxing was continued for 3 hr.

Methyl Phenoxazine-1-carboxylate.—A mixture of 350 mg of **6a**[4] in 90 ml of MeOH was cooled and saturated with dry HCl. The mixture was stirred under reflux for 4 hr and the resulting solution was cooled and diluted with H_2O. The MeOH was distilled and the aqueous residue was extracted (Et_2O). The ether was washed (5% $NaHCO_3$, H_2O), dried ($MgSO_4$), and distilled. The residue was sublimed and recrystallized from EtOH–H_2O to give 200 mg of ester, mp 128–129°. *Anal.* ($C_{14}H_{11}NO_3$) C, H, N.

The methyl ester prepared from **6a** obtained from the cyclization route melted at 127–128° (EtOH). *Anal.* ($C_{14}H_{11}NO_3$) C, H, N.

3-(2-Amino-3-carboxyphenoxy)-2-chlorobenzoic Acid.—A mixture of **5b** and 5 *N* KOH was heated 2 hr on a steam bath. The solution was filtered, cooled, and neturalized. The solid was filtered, washed with H_2O, dried, and recrystallized from EtOAc, mp 273° dec. *Anal.* ($C_{14}H_{10}ClNO_5$) C, H, Cl, N.

Acknowledgment.—We wish to thank Dr. James H. Birnie for the biological test data and members of the Analytical and Physical Chemistry Section, Smith Kline and French Laboratories, for elemental analyses. We would also like to thank Miss Suzanne R. Cohen for preparing **3p** and the methyl ester of **6a**.

Hypotensive Activity of Some Cyanoguanidines

SHREEKRISHNA M. GADEKAR, SOPHIA NIBI, AND ELLIOTT COHEN

Organic Chemical Research Section, Lederle Laboratories, A Division of American Cyanamid Company, Pearl River, New York 10965

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A series of substituted cyanoguanidines was synthesized and screened for hypotensive activity. One of these, 1-*t*-amyl-3-cyanoguanidine (**2**), was selected for further animal studies.

Several years ago 1-*t*-butyl-3-cyanoguanidine[1] (**1**) was found to have appreciable hypotensive activity in a random screening test carried out in normotensive rats.[2] Since the simple unbranched homologs were devoid of activity, and we were not aware of any reported hypotensive activity for cyanoguanidines, we set out to prepare a number of analogous compounds. There are, of course, many examples in the literature of guanidine derivatives possessing hypotensive activities.[3] This report deals with the synthesis and hypotensive activity of the series of substituted cyanoguanidines listed in Table I.

Chemistry.—The synthesis of monosubstituted cyanoguanidines was accomplished by a well-established procedure[4] consisting of the condensation of the hydrochloride of the appropriate amine with sodium (or lithium) dicyanamide. The reactions were carried out in either 1-butanol or in H_2O. In a few cases the choice of solvent was critical.

$$RNH_2{\cdot}HCl + NaN(CN)_2 \longrightarrow RNHC(=NCN)NH_2 + NaCl$$

To prepare compounds with substituents on both nitrogens, two additional methods were employed. In the first case, heating a mixture of 1-cyano-2,3-dimethyl-2-thiopseudourea, *t*-butylamine, and ethanol in an autoclave yielded 1-*t*-butyl-2-cyano-3-methylguanidine (**17**). This procedure has been used by Curd to prepare substituted dicyandiamides.[4]

(1) R. M. Acheson, G. A. Taylor, and M. L. Tomlinson, *J. Chem. Soc.*, 3750 (1958).

(2) J. R. Cummings, J. L. Grace, and C. N. Latimer, *J. Pharmacol. Exp. Ther.*, **141**, 349 (1963). The test compounds (100 mg/kg) were suspended in 2% starch and administered to conscious rats by gavage. Mean arterial blood pressure was measured 2 hr later.

(3) (a) E. Schlittler, J. Druey, and A. Marxer, *Progr. Drug Res.*, **4**, 341 (1962); (b) H. Najer, R. Giudicelli, and J. Seite, *Bull. Soc. Chim. France*, 1593 (1962); (c) J. H. Short, U. Biermacher, D. A. Dunnigan, and T. D. Leth, *J. Med. Chem.*, **6**, 275 (1963); (d) J. Augstein, S. M. Green, A. M. Monro, G. W. H. Potter, C. R. Wortbing, and T. I. Wrigley, *ibid.*, **8**, 446 (1965); (e) R. P. Mull, R. H. Mizzoni, M. R. Dapero, and M. E. Egbert, *ibid.*, **5**, 944 (1962).

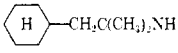
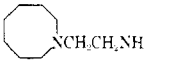
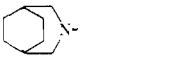
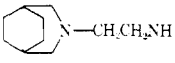
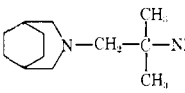
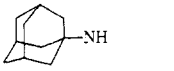
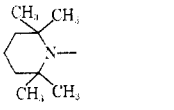
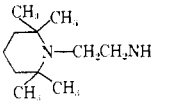
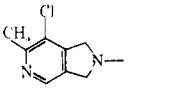
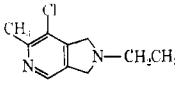
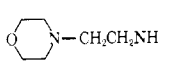
(4) F. H. S. Curd, J. A. Hendry, T. S. Kenny, A. G. Murry, and F. L. Rose, *J. Chem. Soc.*, 1630 (1948).

TABLE I

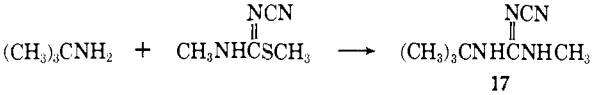
CYANOGUANIDINES

NCN

RCNHR′

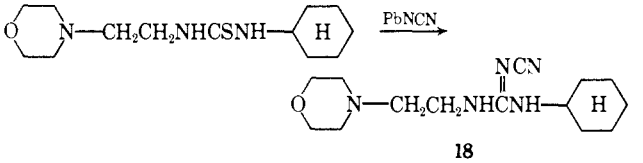
No.	R	R′	Yield, %	Mp, °C	Formula	Analyses
1	$(CH_3)_3CNH$	H	49[a]	192–194[c]	$C_8H_{12}N_4$	
2	$C_2H_5C(CH_3)_2NH$	H	57[a]	154–156	$C_7H_{14}N_4$	C, H, N
3	$(CH_3)_3CCH_2NH$	H	45[a]	182–183	$C_7H_{14}N_4$	C, H, N
4	$[(CH_3)_3C]_2N$	H	41[a]	184–185	$C_{10}H_{20}N_4$	C, H, N
5	p-$ClC_6H_4CH_2C(CH_3)_2NH$	H	62[a]	198–199	$C_{12}H_{15}ClN_4$	C, H, N
6		H	32[b]	147–148	$C_{12}H_{22}N_4$	C, H, N
7		H	16[b]	123–125	$C_{11}H_{21}N_5$	C, H, N
8		H	68[b]	245–246	$C_{10}H_{16}N_4$	C, H; N[d]
9		H	59[b]	178–179	$C_{12}H_{21}N_5$	C, H; N[e]
10		H	30[b]	178–180	$C_{14}H_{25}N_5$	C, H; N[f]
11		H	36[b]	110–112	$C_5H_8N_4$	C, H, N
12		H	80[a]	277–279	$C_{12}H_{18}N_4$	C, H, N
13		H	70[b]	183–184	$C_{11}H_{23}N_4$	C, H, N
14		H	41[b]	171–172	$C_{13}H_{28}N_5$	C, H, N
15		H	72[b]	280–281	$C_{10}H_{10}ClN_5 \cdot 0.5H_2O$	C, H, N
16		H	21[b]	188–189	$C_{12}H_{15}ClN_6$	C, H; N[g]
17	$(CH_3)_3CNH$	CH_3	18	171–172	$C_7H_{14}N_4$	C, H, N
18			50	172–174	$C_{14}H_{25}N_5O$	C, H, N

[a] Reaction solvent 1-BuOH. [b] Water. [c] Lit.[4] mp 188–189°. [d] N: calcd, 29.2; found, 28.5. [e] N: calcd, 29.8; found, 29.3. [f] N: calcd, 26.6; found, 25.6. This sample was analyzed by Schwarzkopf Microanalytical Laboratory, Woodside, N. Y. [g] N: calcd, 30.2; found, 29.7.



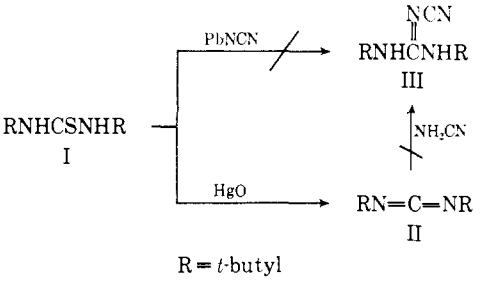
17

The synthesis of 1-cyclohexyl-2-cyano-3-(morpholinoethyl)guanidine (**18**) was accomplished by the procedure of Lecher, *et al.*, which uses a thiourea with lead cyanamide.[5]



18

The preceding reaction procedure was employed in an attempt to prepare the di-*t*-butyl product III. However, the bulky *t*-butyl groups apparently hindered the reaction. The carbodiimide II, prepared from the corresponding thiourea I by the method of Schmidt,[6] on treatment with cyanamide also failed to form III.



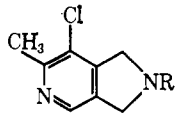
R = *t*-butyl

In order to compare the activities of the cyanoguanidines **15** and **16** with their respective guanidines the amines used in the preparations of **15** and **16** were

(5) H. Z. Lecher, R. P. Parker, and R. S. Long, U. S. Patents 2,438,124 and 2,455,804 (1948).

(6) E. Schmidt, W. Striwsky, and F. Hitzler, *Ann.*, **560**, 222 (1948).

guanylated by the method of Rathke[7] to yield products **19** and **20**.



19, R = C(=NH)NH$_2$
20, R = CH$_2$CH$_2$NC(=NH)NH$_2$

Most of the amine intermediates used in these syntheses were known compounds. All new preparations or modifications of existing procedures are described in the Experimental Section.

The methods used to screen and evaluate compounds for hypotensive activity have been previously described.[2]

Pharmacological Activity.—Seven of the reported compounds (**1–4** and **13–15**) were found active as hypotensive agents in rats (*i.e.*, a 30-mm or more drop in blood pressure). It has been reported that guanylation of certain hypotensive amines possessing ganglioplegic action results in the retention of the hypotensive effect and loss of the undesired ganglion-blocking activity.[8] When the corresponding cyanoguanidines were prepared, in three cases (**8–10**) no activity was found and in two cases (**13** and **14**) the products were, indeed, hypotensive but still possessed ganglion-blocking activity. Compound **15**, like **1–4**, was devoid of ganglioplegic activity.

The reported hypotensive activity of *t*-butylguanidine[3c] (with its obvious similarity to **1**) prompted us to prepare the "cyano" analog **7** of guanethidine. However, it was devoid of activity. In a similar fashion, since **15** was active, the guanidines **19** and **20** were prepared but they were also inactive as hypotensives.

Slight variations of structure **1** such as an additional methyl group on the terminal nitrogen (see **17**) or gross changes leading to an adamantylamine derivative (see **12**) resulted in total loss of activity.

Most of the other variations were chosen to provide highly branched groups adjacent to the nitrogen (*e.g.*, **5**, **6**, and **10**) but none of these compounds possessed any activity.

The most active compound, 1-*t*-amyl-3-cyanoguanidine[9] (guancydine, **2**) was selected for further evaluation in animals.[10]

Experimental Section

The melting points were determined in open capillary tubes and are uncorrected. Where analyses are indicated only by symbols of the elements, analytical results obtained for those elements were within ±0.4% of the theoretical values.

α,α-Dimethylcyclohexaneethylamine (IV).—A mixture containing 9.2 g (0.05 mole) of β-(*p*-chlorophenyl)-α,α-dimethylethylamine, 0.25 g of PtO_2, and 100 ml of AcOH (glacial) was hydrogenated at room temperature and pressure for 2 hr. There was practically no uptake of H_2. An additional 0.5 g of the catalyst was added and hydrogenation was continued for 5 more hr, but at 80°. Only 10% of the required uptake of hydrogen resulted. Finally a large amount (1.5 g) of the catalyst was added and the reduction was continued for 6 hr at 60–65° until the theoretical amount of H_2 was consumed. The catalyst was removed by filtration, and the filtrate was evaporated *in vacuo* to a syrup. This was dissolved in 50 ml of H_2O made alkaline and extracted with Et_2O. The distillation of the extract *in vacuo* provided 5.4 g (69%) of a fraction boiling at 42–45° (0.4 mm), $n^{23}D$ 1.5950. *Anal.* ($C_{10}H_{21}N_2$) C, H, N.

3-Azabicyclo[3.3.2]nonane-3-acetonitrile (V).—A solution containing 3.5 g (0.028 mole) of 3-azabicyclo[3.3.2]nonane, 2.1 g (0.028 mole) of 75% aqueous glycolonitrile, and 20 ml of EtOH was refluxed for 4 hr. A brown oil was obtained on evaporation of the mixture *in vacuo* which soon solidified to give 3.5 g (76%) of a crystalline compound, mp 51–52°; recrystallized from EtOH, mp 59–60°. *Anal.* ($C_{10}H_{16}N_2$) C, H, N.

1-Cyanomethyl-2,2,6,6-tetramethylpiperidine (VI).—Following the procedure described in the preceding preparation this nitrile was prepared from the corresponding amine[11] in a 55% yield, mp 39–40°. *Anal.* ($C_{11}H_{20}N_2$) C, H; N: calcd, 15.5; found, 16.0.

The method was applicable also to the preparation of 7-chloro-6-methyl-1,3-dihydro-2H-pyrrolo[3,4-*c*]pyridine-2-acetonitrile (VII) from the analogous secondary amine.[12] A 49% yield of a crystalline material, mp 90–91°, from petroleum ether, was obtained. *Anal.* ($C_{10}H_{10}ClN_3$) C, H, N.

2-Aminoethyl-7-chloro-6-methyl-1,3-dihydro-2H-pyrrolo[3,4-*c*]pyridine Trihydrochloride (VIII).—To a suspension of 0.38 g (0.010 mole) of $LiAlH_4$ in 35 ml of anhydrous Et_2O was added a solution of 1.04 g (0.005 mole) of 7-chloro-6-methyl-1,3-dihydro-2H-pyrrolo[3,4-*c*]pyridine-2-acetonitrile in 45 ml of Et_2O. The mixture was refluxed for 6 hr, cooled in an ice bath, and then treated with 0.8 ml of 7.5% NaOH and 1.2 ml of H_2O. The suspension was filtered and the solvent was removed *in vacuo*. The resultant oil was converted to the trihydrochloride with ethanolic HCl and Et_2O to give 0.73 g (45%) of a yellow solid. The hygroscopic salt was recrystallized from a mixture of MeOH, EtOH, and Et_2O; mp 255–257° dec. *Anal.* ($C_{10}H_{14}ClN_3 \cdot 3HCl$) C, H, N.

3-(2-Aminoethyl)azabicyclo[3.2.2]nonane dihydrochloride (IX) was similarly prepared from the corresponding nitrile. The base which boiled at 80–82° (0.75 mm) was obtained in 86% yield: mp >300° as a dihydrochloride. *Anal.* ($C_{10}H_{20}N_2 \cdot 2HCl$) C, H, N.

1-(2-Aminoethyl)-2,2,6,6-tetramethylpiperidine Dihydrochloride (X).—The $LiAlH_4$ reduction of the corresponding nitrile provided this diamine as a base in 54% yield, mp 252–253° as dihydrochloride. *Anal.* ($C_{11}H_{24}N_2 \cdot 2HCl$) C, H, N.

3-(2-Methyl-2-nitropropyl)-3-azabicylo[3.2.2]nonane (XI).[13]—A solution containing 25 g (0.2 mole) of 3-azabicyclo[3.2.2]-nonane, 17.8 g (0.2 mole) of 2-nitropropane, and 60 ml of 1,4-dioxane was treated at 0–3° with 16.2 g of (37%) aqueous H_2CO and 8 ml of (2%) NaOH. The mixture was stirred for 1 hr and then heated over steam for another 1 hr. Addition of 100 ml of H_2O to the cooled mixture afforded a semisoft solid, mp 68–72°; recrystallized from EtOH, 29.1 g (64%), mp 72–73°. *Anal.* ($C_{12}H_{22}N_2O_2$) C, H, N.

3-(2-Amino-2-methylpropyl)-3-azabicyclo[3.2.2]nonane Dihydrochloride (XII).—A solution of 13 g (0.057 mole) of the nitroamine in 115 ml of MeOH was hydrogenated with 1.15 g of Ra(Ni) at 77.33 kg/cm^2 pressure. Another 0.5 g of the catalyst was added 3 hr later and the reduction was continued for a total of 6 hr when 92% of the theoretical amount of H_2 was consumed. After removal of the catalyst the fitrate was cooled and saturated with HCl gas. Evaporation of MeOH gave a brown residue which on recrystallization from EtOH gave 6.3 g (41%) of the dihydrochloride, mp 283–285°. *Anal.* ($C_{12}H_{24}N_2 \cdot 2HCl$) C, H, N.

1-*t*-Butyl-3-cyanoguanidine[1] (1).—A mixture of 110 g (1.00 mole) of *t*-butylamine hydrochloride, 80 g (1.00 mole) of lithium dicyanamide (94% purity), and 500 ml of *n*-BuOH was refluxed with stirring for 18 hr. The mixture was cooled to 0° and the salt was filtered and washed with 100 ml of EtOH. The combined filtrate was concentrated to a slurry *in vacuo*, dissolved in

(7) B. Rathke, *Ber.*, **14**, 1774 (1881).

(8) (a) Farbenfabriken Bayer A.G., Belgian Patents 607,479 and 608,905 (1961). (b) The hypotensive and ganglion blocking effects of the amines were reported by S. Rossi, C. Valvo, and W. Britta, *Gazz. Chim. Ital.*, **89**, 1164 (1959). In our tests, the amines used to prepare **8–10** were found inactive as hypotensives.

(9) This compound was originally prepared by Dr. D. E. Nagy at Stamford Laboratories Division of American Cyanamid Co.

(10) J. R. Cummings, A. N. Welter, J. L. Grace, Jr., and L. M. Lipchuck, *J. Pharmacol. Exp. Ther.*, in press.

(11) N. J. Leonard and E. W. Nommensen, *J. Am. Chem. Soc.*, **71**, 2808 (1949).

(12) S. M. Gadekar, J. L. Frederick, J. Semb, and J. R. Vaughan, Jr., *J. Org. Chem.*, **26**, 468 (1961).

(13) G. B. Butler and F. N. McMillan, *J. Am. Chem. Soc.*, **72**, 2978 (1950).

200 ml of hot EtOH, and clarified, H_2O was added, and the cyanoguanidine (1) precipitated.

Using a similar procedure and the same molar quantities of the reactants, 1-*t*-amyl-3-cyanoguanidine (**2**) was prepared from the corresponding amine hydrochloride.

N-Cyano-3-carboxamidino-3-azabicyclo[3.2.2]nonane (8).—To a solution of 1.25 g of the azabicyclononane in 1 ml of concentrated HCl and 4 ml of H_2O was added 0.9 g (0.01 mole) of sodium dicyanamide. The mixture was refluxed for 2 hr; however, within 20 min of refluxing a solid had precipitated. The reaction mixture was cooled and the solid was filtered off and recrystallized from aqueous EtOH.

1-*t*-Butyl-2-cyano-3-methylguanidine (17).—A steel autoclave equipped with a glass liner was charged with 3.2 g (0.025 mole) of 1-cyano-2,3-dimethyl-2-thiopseudourea, 15 ml of *t*-butylamine, and 60 ml of EtOH and was heated at 125° for 6 hr. The vessel was cooled, and the light brown solution was removed and evaporated to a syrup. When this syrup was dissolved in a 50% EtOH–H_2O mixture by warming and the solution was decolorized with charcoal, 0.2 g of an unidentified material melting at 201–211° was obtained. The filtrate from it, on further dilution with 30 ml of H_2O, gave 0.7 g of the desired product. It was recrystallized from dilute EtOH.

1-Cyclohexyl-2-cyano-3-(2-morpholinoethyl)guanidine (18).—A mixture containing 2.61 g (0.009 mole) of 1-cyclohexyl-3-(2-morpholinoethyl)thiourea (Aldrich Chemical Co.), 2.72 g (0.011 mole) of lead cyanamide, and 16 ml of EtOH was stirred and refluxed for 18 hr. The reaction was not complete as observed by the formation of mercuric sulfide when a clarified aliquot of the mixture was heated with yellow mercuric oxide. Another 0.5 g of PbNCN was added to the reaction mixture and refluxing was continued for 7 hr longer. The precipitated sulfide was filtered off and the cyanoguanidine was isolated by cooling the filtrate. It was recrystallized from EtOH.

The physical constants, yields, and other pertinent data for the individual compounds are given in Table I.

7-Chloro-1,3-dihydro-6-methyl-2H-pyrrolo[3,4-c]pyridine-2-carboxamidine Dihydrochloride (19).—A mixture containing 6.7 g (0.04 mole) of 7-chloro-6-methylmerimine,[12] 5.6 g (0.02 mole) of S-methylpseudothiourea sulfate, and 30 ml of H_2O was refluxed for 18 hr. The hot mixture was decolorized with charcoal and filtered. A solid which precipitated on cooling was filtered and dried. A satisfactory elemental analysis for the sulfate of the desired compound could not be obtained even after repeated recrystallizations. By neutralizing an aqueous solution of the sulfate with $NaHCO_3$ and then dissolving it in ethanolic HCl 2.5 g (22%) of the dihydrochloride was obtained; recrystallized from 95% EtOH, mp 285–295° dec. *Anal.* ($C_9H_{11}ClN_4 \cdot 2HCl$) C, H, N.

1-[2-(7-Chloro-1,3-dihydro-6-methyl-2H-pyrrolo[3,4-c]pyridine-2-yl)ethyl]guanidine Sulfate Hemihydrate (20).—A mixture containing 1.06 g (0.005 mole) of the base of the merimine used in the preparation of **16**, 0.7 g (0.0025 mole) of 2-methylthiopseudourea sulfate, and 5 ml of H_2O was refluxed for 8 hr. The solid which precipitated on cooling was filtered, washed with cold H_2O, and dried to yield 0.93 g (60%), mp 217–221°; recrystallized from MeOH and Et_2O, mp 219–222°. *Anal.* [($C_{10}H_{16}ClN_5$)$_2$·H_2SO_4·H_2O] C, H, N.

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The Synthesis and Activity of Some 2,6-Difluorophenyl-Substituted Compounds

A. M. ROE, R. A. BURTON, G. L. WILLEY, M. W. BAINES, AND A. C. RASMUSSEN

Smith Kline and French Research Institute, Welwyn Garden City, Hertfordshire, England

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The preparation of 2,6-difluorophenyllithium, and its conversion into a range of 2,6-difluoroaromatic compounds (see Chart I), has led to the synthesis of several difluoro analogs of known pharmacologically active compounds such as lidocaine and xylocholine. Their local anesthetic activity, adrenergic neurone blocking activity, nicotinic activity, and some of the effects that these compounds have on the behavior of conscious mice are reported and discussed.

A wide variety of pharmacologically active 1,2,3-trisubstituted aromatic compounds in which the 1 and 3 substituents are chlorine or methyl have been described. These include the local anesthetics lidocaine (**28**),[1] 2-(2,6-dichlorophenoxy)ethyldimethylamine (**14**), and xylocholine (**19**), and the adrenergic neurone blocking drugs xylocholine (**19**) and its guanidino analog (**11**).

This paper describes the completion of the series of compounds to which the foregoing belong by the synthesis of the 2,6-difluorophenyl analogs, and we report a study of the comparative pharmacology of the unsubstituted, the difluoro, the dichloro, and the dimethyl compounds (Table I). A series of related ureas has also been prepared and tested for their effect on the behavior of conscious mice.

2,6-Difluorobenzoic acid[2] and 2,6-difluorophenol[3] are both known compounds, but when this investigation started, they were not easily prepared in quantity. We therefore set out to find a convenient and suitably versatile synthesis for these and other 2,6-difluoroaryl compounds. The employment of an aryllithium intermediate seemed feasible,[4] and we found that 1,3-difluorobenzene in tetrahydrofuran, or in mixtures of THF and hexane or heptane (2:1–4:1), formed a stable aryllithium (I) when treated with *n*-butyllithium at below −50°. This was demonstrated by the formation of 2,6-difluorobenzoic acid (II) in 81% yield after

(1) The compounds studied in this work have been assigned the numbers shown in Table I. Pertinent references to the origin of the compound and, if previously described, to its pharmacology are given in the footnotes to Table I.

(2) J. Thomas and J. Canty, *J. Pharm. Pharmacol.*, **14**, 587 (1962).

(3) G. C. Finger, M. J. Gortatowski, R. H. Shiley, and R. H. White, *J. Am. Chem. Soc.*, **81**, 94 (1959).

(4) We are grateful to Dr. J. N. Gardner for suggesting this reaction to us. H. Gilman and T. S. Soddy, *J. Org. Chem.*, **22**, 1715 (1957), converted fluorobenzene into 2-fluorophenyllithium, which was stable in THF at −60°, and then into 2-fluorobenzoic acid. G. Wittig and W. Merkle, *Ber.*, **75**, 1491 (1942), demonstrated that 1,3-difluorobenzene was metallated by phenyl- or by methyllithium in ether; the products of their reactions, which were conducted at −15 or 0°, were consistent with the formation of a substituted benzyne from a putative 2,6-difluorophenyllithium. J. Hine and P. B. Langford, *J. Org. Chem.*, **27**, 4149 (1962), demonstrated the acidity of the hydrogen at the 2-carbon in 1,3-difluorobenzene by deuterium exchange studies.